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NOVAK DRUCE DELUCA + QUIGG LLP
1300 EYE STREET NW
SUITE 1000 WEST TOWER
WASHINGTON, DC 20005

EXAMINER	
WESSENDORF, TERESA D	

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BERNHARD HAUER, ROLF D. SCHMID, MARKUS ENZELBERGER, and STEPHAN MINNING

Appeal 2008-5887
Application 09/674,962
Technology Center 1600

Decided: December 22, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS, and DEMETRA J. MILLS, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 5-9, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a peptide. Claim 5 is illustrative:

5. A peptide comprising SEQ ID NO: 1, in which the variables X^1 to X^6 have the following meanings:

X^1 = Asn;

X^2 = Gln, Glu or Arg;

X^3 = Gly, Thr or Tyr;

X^4 = Asn or Arg;

X^5 = Gly or Lys;

X^6 = Cys.

The Examiner relies on the following prior art references to show unpatentability:

Guerinot et al.	US 5,846,821	Dec. 8, 1998
Haymore et al.	EP 0 409 814 A1	Jan. 23, 1991

Volz et al., *Molecular characterization of metal-binding polypeptide domains by electrospray ionization mass spectrometry and metal chelate affinity chromatography*, 800 J. CHROMATOGRAPHY 29-37 (1998).

The rejection as presented by the Examiner is as follows:

Claims 5-9 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Volz, Guerinot and Haymore.

We affirm.

ISSUE

Does the combination of Volz, Guerinot, and Haymore teach a peptide comprising His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO: 1); wherein

X^1 = Asn; X^2 = Gln, Glu or Arg; X^3 = Gly, Thr or Tyr; X^4 = Asn or Arg; X^5 = Gly or Lys; X^6 = Cys?

FINDINGS OF FACT

1. This Appeal is related to Appeal No. 2005-2596 (the 2596 Appeal). On April 28, 2006 a Decision was entered in Appeal No. 2005-2596 affirming the rejection under 35 U.S.C § 103(a) as unpatentable over the combination of Volz, Guerinot and Haymore (Decision 7). In the 2596 Appeal, then pending claims 1-4 were before the Board (Decision 1). The claims were not separately argued, therefore the Merits Panel limited their review to representative claim 1, reproduced below:

> 1. A peptide fragment having the general sequence His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO:1), where the variables X^1 to X^6 in the sequence have the following meanings:
>
> X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys and the variables X^2 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or
>
> X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg and the variables X^1, X^3 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or
>
> X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and the variables X^1, X^2, X^4 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or
>
> X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His and the variables X^1 to X^3, X^5, X^6 an amino acid selected from the

> group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or
>
> X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg and the variables X^1 to X^4, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or
>
> X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln and the variables X^1 to X^5 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and
>
> where at least one of the variables X^1 to X^6 in the sequence is, independently [sic, independent] of one another, Gln or Asn.

(Decision 1-2).

2. Claim 5, before us in this Appeal, is directed to a peptide comprising the sequence His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO: 1) (Claim 5 and Spec. 13: 5 (as amended July 1, 2002). Claim 5 defines variables X^1 to X^6 have the following meanings: X^1 = Asn; X^2 = Gln, Glu or Arg; X^3 = Gly, Thr or Tyr; X^4 = Asn or Arg; X^5 = Gly or Lys; X^6 = Cys (Claim 5). Thus, the peptide of claim 5 is a species of the peptide set forth in claim 1 of the 2596 Appeal.

3. Volz teaches "that peptides containing H[is]-X-H[is] sequences bind with high affinity to nickel (Ni^{2+}) and copper (Cu^{2+}) ions" (Decision 4). Volz teaches "that C-X-X-C sequences, which are present in zinc finger proteins, bind to Cu^{2+}, Zn^{2+} and Ni^{2+}" (*id.*). Volz teaches that *Helicobacter pylori* "ATPase-439 (1-51) contain[s] a HxHxxxCxxC motif" (Volz 32, col. 2, ll. 33-34). Volz teaches that ATPase-439 has high affinity to both Ni^{2+} and Cu^{2+} ions (Volz 32, col. 2, ll. 46-47; Decision 4). Volz reports the

sequence of ATPase-439 (1-51) as MQEYHIHNLD CPDCASKLER DLNKDYVKK AQINFSTSRL FLDTSDFEKV K (Volz 34; Fig. 2a (emphasis added to illustrate the HxHxxxCxxC motif)). Therefore, Volz teaches a peptide comprising the sequence His-Ile-His-Asn-Leu-Asp-Cys-Pro-Asp-Cys. Stated differently Volz teaches a peptide comprising the sequence His-X^a-His-X^b-X^c-X^d-Cys-X^e-X^f-Cys; wherein X^a is Ile, X^b is Asn, X^c is Leu, X^d is Asp, X^e is Pro, and X^f is Asp.

4. Guerinot teaches members of the MRT family of polypeptides that are "capable of transporting metals such as Fe(II), Cd, Co, Mn, Pb, Hg and Zn" (Guerinot, Abstract). Guerinot teaches that "conservative amino acid substitutions . . . [can be] made at one or more predicted non-essential amino acid residues" of these proteins (Guerinot, col. 14, ll. 16-18). Guerinot teaches that "[a] 'non-essential' amino acid residue is a residue that can be altered from the wild-type sequence of MRT . . . without altering the MRT activity of the polypeptide" (Guerinot, col. 13, l. 65 - col. 14, l. 3). Guerinot teaches that

> A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

(Guerinot, col. 14, ll. 18-30.) According to Guerinot,

> a predicted nonessential amino acid residue in MRT is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an MRT coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for proteolytic activity to identify mutants that retain proteolytic activity.

(Guerinot, col. 14, ll. 30-37.)

5. Haymore teaches "proteins and polypeptides having an enhanced affinity, i.e. greater binding strength, for immobilized-metal affinity resins" (Haymore, Abstract). Haymore teaches that the protein's or polypeptide's metal-chelating sequence can be represented by the formula:

> -A-B_x-C_y-D_z[-]E wherein A and E are independently metal-binding amino acids selected from the group consisting of histidine and aspartate provided that at least one of either A or E is histidine, B, C and D are amino acids, and x, y and z are integers from 0 to 3 depending on the secondary structure of the surface exposed portion of the protein or polypeptide molecule which includes the metal-chelating or sequence-containing site and the particular metal-binding amino acids utilized in the metal chelating sequence.

(Haymore 3: 28-33). Stated differently, Haymore teaches a His-X_{0-3}-His(Asp) or His(Asp)-X_{0-3}-His motif. According to Haymore, "[t]he nature of the intervening residues ('X') is relatively unimportant; the modeling demonstrated that the steric size, the hydrophaticity and the charge of the sidechains of these residues play only minor or secondary roles in determining the strength of the metal-chelating peptide interactions" (Haymore 4: 10-13).

PRINCIPLES OF LAW

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. On appeal to this Board, Appellants must show that the Examiner has not sustained the required burden.[1]

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at 1742. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 1741. *See also id.* at 1742 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of

[1] *See* (1) *Ex parte Yamaguchi*, Appeal 2007-4412, slip op. at 5 and 23 (BPAI Aug. 29, 2008); (2) *Ex parte Fu*, Appeal 2008-0601, slip op. at 5 and 20 (BPAI Mar. 31, 2008); (3) *Ex parte Catan*, Appeal 2007-0820, slip op. at 3 and 21 (BPAI Jul. 3, 2007) and (4) *Ex parte Smith*, Appeal 2007-1925, slip op. at 4, 9 and 23 (BPAI Jun. 25, 2007). Opinions in support of the decisions in these four appeals are (a) precedential opinions of the Board and (b) available on the USPTO website.

ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

The reason to combine the teachings of the applied prior art does not have to be the same as that of the appellants. *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996) ("the motivation in the prior art to combine the references does not have to be identical to that of the applicant to establish obviousness."). *See also In re Geisler*, 116 F.3d 1465, 1470, (Fed. Cir. 1997) ("'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'") (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).

> Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references.

DyStar Textilfarben GMBH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1368 (Fed. Cir. 2006).

Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii) ("Any arguments or authorities not included in the brief or a reply brief ... will be refused consideration by the Board, unless good cause is shown.").

ANALYSIS

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 5 is representative.

Based on the combined teachings of Volz, Guerinot, and Haymore (FF 3-5) the Examiner concludes that the noncritical or intervening residues between the His and Cys metal binding residues are relatively unimportant to the peptides ability to bind metal ions (Ans. 4). As the Board previously explained in their Decision

> "Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues." In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a H-X-H-X-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important.

(Decision 8; Ans. 5.) "Accordingly, the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif" (Ans. 5). In this regard, the Examiner finds that "[o]ne would reasonably expect successful binding of the peptide fragments to metal ions since all of the prior art teaches the metal binding resides in the critical His and Cys residues of the motif" (Ans. 4).

Appellants contend that "random substitution is wholly contrary to the principles of the claimed invention, which is directed to providing novel peptide fragments that exhibit increased protein selectivity and simplification of protein purification when compared with known fragments" (App. Br. 4-5). We are not persuaded. The reason to combine

the teachings of the applied prior art does not have to be the same as that of the appellants. *In re Kemps*, 97 F.3d at 1430 ("the motivation in the prior art to combine the references does not have to be identical to that of the applicant to establish obviousness").

Volz teaches a peptide comprising SEQ ID NO: 1 having metal binding properties (FF 3). While it is true that the "X" residues of Volz's sequence are not the same as those set forth in claim 5 (*id.*); Haymore teaches that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide (FF 5). Guerinot teaches that these non-critical amino acid residues can be modified by either making conservative substitutions or by random mutagenesis followed by screening (FF 4).

There is no requirement in Appellants' claim 5 that the peptide exhibit increased protein selectivity or that it simplify protein purification compared with known fragments. Nevertheless, it would have been prima facie obvious to optimize those amino acid residues in the non-critical regions of the peptide to enhance the ability of the peptide to bind metal. *In re Geisler*, 116 F.3d at 1470 ("'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'") (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).

Appellants contend that "there is simply no teaching or suggestion to substitute an amino acid of one side chain family with an amino acid from another side chain family or to simply pick and choose from among the 20 naturally occurring amino acids for each of positions X^1-X^6" (App. Br. 5-6). We are not persuaded.

Not only does Guerinot teach the selection of conservative amino acid substitutions from specific side chain families, Guerinot also teaches random mutagenesis followed by screening to identify peptides that exhibit variability in the non-critical regions of the peptide's sequence, which Haymore teaches are relatively unimportant (FF 4 and 5).

Appellants contend that "according to Haymore et al., substitution of an intervening amino acid denominated as 'X' would result in no change in the metal binding activity of the peptide" thus the prior art "suggests that any attempt to substitute an intervening amino acid denominated by 'X' would yield no material effect metal binding properties and would be futile in nature" (App. Br. 7-8). We are not persuaded. Appellants' contention is in direct conflict with Guerinot's mutation of non-essential amino acid residues in MRT that do not altering the MRT activity of the polypeptide (FF 4).

Appellants contend that they "ha[ve] identified the problem of increased protein selectivity and simplification of protein purification (page 3, lines 1-7 of the instant application), which problem was not recognized by one of ordinary skill in the art" (App. Br. 10). We are not persuaded. The claimed invention is drawn to a peptide not a method (FF 2). Furthermore, Appellants' Specification discloses that the selectivity and purification of proteins can be accomplished by a large genus of peptides of the general formula set forth in SEQ ID NO: 1, which the peptide of claim 5 falls within (Spec. 3: 7 - 14: 7; FF 1). Appellants fail to direct our attention to any teaching in their Specification that would support a finding that the peptides within the scope of claim 5 exhibit some unexpected property relative to the larger genus of peptides taught by their Specification. Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Further, as discussed above, Guerinot teaches random mutagenesis followed by screening to identify peptides that exhibit variability in the non-critical regions of the peptide's sequence, which Haymore teaches are relatively unimportant (FF 4 and 5). "Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves." *Dystar*, 464 F.3d at 1368. Accordingly, we are not persuaded by Appellants' contention that Guerinot does not describe or suggest uses beyond its primary purpose of improving metal-regulated transporters and is limited to the use of conservative substitutions from the same side chain family (App. Br. 10).

Appellants contend that the prior art "do[e]s not disclose, teach or suggest that substitution of the intervening amino acid residue 'X' would be a desirable modification to increase the metal binding activity of the peptide" (*id.*). There is, however, no requirement in claim 5 that the peptide have an increased metal binding activity, or that the peptides actually have the increased metal binding activity asserted. Therefore, "[i]n such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references." *Dystar*, 464 F.3d at 1368. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S. Ct. at 1741. The *KSR* reason for changing one non-essential amino acid to another is provided by the prior art and it would therefore be obvious to try any amino acid in any of the non-essential amino acid positions (FF 4 and 5).

CONCLUSION OF LAW

The combination of Volz, Guerinot, and Haymore teaches a genus of peptides comprising His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO: 1), including those wherein X^1 = Asn; X^2 = Gln, Glu or Arg; X^3 = Gly, Thr or Tyr; X^4 = Asn or Arg; X^5 = Gly or Lys; X^6 = Cys. There is no evidence on this record that peptides within the scope of claim 5 exhibit superior properties relative to other metal binding peptides that fall within the genus taught by the combination of prior art relied upon by the Examiner. Thus, the preponderance of the evidence on this record falls in favor of the Examiner.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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NOVAK DRUCE DELUCA + QUIGG LLP
1300 EYE STREET NW
SUITE 1000 WEST TOWER
WASHINGTON DC 20005